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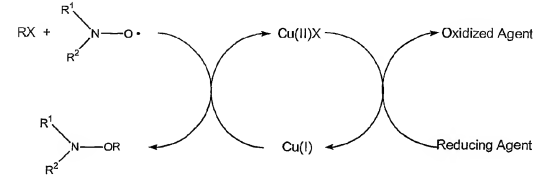
(54) Title: PREPARATION OF ALKOXYAMINES



(57) Abstract: Embodiments of the process for the preparation of alkoxyamines of the present invention are directed to conducting a coupling reaction in a reaction medium initially comprising at least one transition metal catalyst, an ATRP initiator and a nitroxide or nitroxide precursor. The reaction medium may additionally comprise a reducing agent. In certain embodiments the reducing agent is the nitroxide precursor. The reducing agent may be added initially or during the coupling process in a continuous or intermittent manner. The coupling process may further comprises reacting the reducing agent with at least one of the transition metal catalyst in an oxidized state further comprising a radically transferable atom or group to form a compound that does not participate significantly in control of the coupling process. Embodiments of the present invention comprise reacting a reducing agent with at least one of catalyst in an oxidized state and an ATRP initiator to initiate and/or maintain catalytic activity throughout the coupling process between the formed radical and added nitroxide.

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Preparation of Alkoxyamines

FIELD OF INVENTION

The invention relates to an improved method for the preparation of alkoxyamines and improved methods of conducting atom transfer radical addition or atom transfer radical coupling reactions. In one embodiment, the alkoxyamines may be prepared from nitroxides or nitroxide precursors by conducting an atom transfer radical addition reaction between an ATRP initiator and a stable free radical in the presence of a catalytic amount of a transition metal complex and a reducing agent. In a specific embodiment, an N-hydroxy precursor of a nitroxide can be the reducing agent.

DISCUSSION OF BACKGROUND

Conducting an atom transfer radical coupling (ATRC) reaction to form an alkoxyamine between a molecule comprising a radically transferable atom or group and a stable free radical, such as a nitroxide, in the presence of a transition metal complex is described in United States Patent No. 5,910,549; which is hereby incorporated by reference in its entirety. A stoichiometric amount of a transition metal complex in a lower oxidation state ($Cu^{I}Y/L_n$) is used in the reaction to transfer a radically transferable atom or group from a molecule initially comprising the radically transferable atom (R-X) thereby forming a radical (R*). The radical then reacts with a stable free nitroxide radical, exemplified by TEMPO. The reaction results in an alkoxyamine and the transition metal complex in its higher oxidation state comprising the radically transferable atom or group, ($X\text{-}Cu^{II}Y/L_n$). TEMPO is an archetypal nitroxide and is used herein to exemplify reactions in which any nitroxide can participate, (see Figure 1C).

This ATRC reaction is quantitative and has been employed to study the rate of activation of a series of initiators by various transition metal complexes suitable for an atom

transfer radical polymerization ("ATRP"). ["Determination of Activation and Deactivation Rate Constants of Model Compounds in Atom Transfer Radical Polymerization" Matyjaszewski, K.; Paik, H.-j.; Zhou, P.; Diamanti, S. J. *Macromolecules* **2001**, *34*, 5125-5131. "Determination of activation rate constants in ATRP" Tang, W.; Matyjaszewski, K. *Polymer Preprints*, **2005**, *46(2)* 211; (this abstract also provides some examples of the R-X molecules that can be employed in this reaction) and is further exemplified in a submitted paper.] Indeed, every component of this reaction has been identified and quantified. ["Identification and characterization of monoanionic tripodal tetradentate ligand complexes of copper(I) and (II) involved in atom transfer radical polymerization" Goodwin, J. M.; Olmstead, M. M.; Patten, T. E. *Journal of the American Chemical Society* **2004**, *126*, 14352-14353.] However, as noted above, the ATRC reaction requires at least a stoichiometric amount of the transition metal complex in the lower oxidation state to drive the reaction to completion.

An improvement, that reduced the cost of this process, was disclosed in commonly assigned United States Patent Nos. 6,512,060 and 6,541,580, which are herein incorporated by reference. These patents disclosed the use of a transition metal in the zero oxidation state to drive the reaction between the molecule comprising one or more radically transferable atom or groups ("ATRP initiator") and a transition metal complex in the lower oxidation state to completion. This was accomplished by a reaction between the transition metal in the zero oxidation state and the higher oxidation state transition metal complex to reform the lower oxidation state reactive transition metal complex. ($Cu^0 + Cu^2 \rightarrow 2\ Cu^1$) The ATRP initiator can be a low molecular weight molecule, an oligomer or a polymer. A selection of alkyl halides were converted to alkoxyamines and each reaction showed 100% conversion of the starting alkyl halide and little to no side-products (due to, for example, radical coupling or disproportionation reactions between alkyl radicals) were observed in the proton NMR spectra of the alkoxyamines prior to isolation. All molecules suitable as ATRP initiators are suitable precursors for the dormant segment (R-) of the alkoxyamine. While use of a transition metal in zero oxidation state is less costly than use of a stoichiometric amount of the pure transition metal salt in a lower oxidation state, the final reaction medium still contained a stoichiometric concentration of the transition metal, that is more than 0.5 mole CuX_2 per mole of nitroxide. Optionally, the transition metal may be removed from the reaction product. Thereby adding a significant cost for purification. A variation on these processes was disclosed in United States Patent No. 6,495,720 wherein a specific type of nitroxide was converted to an alkoxyamines. The reaction employs a transition metal

complex comprising ligands, additionally disclosed in United States Patent Nos. 6,512,060 and 6,541,580 and International Patent Application Publication WO 98/40415, to provide more active ATRP catalyst complexes for the coupling reaction.

The first step in these reactions is the formation of a radical species by transfer of the radically transferable atom from the ATRP initiator. In the absence of a stable free radical and in the presence of monomers an ATRP ensues. Indeed, ATRP is considered to be one of the most successful controlled/"living" radical processes (CRP) and has been thoroughly described in a series of co-assigned U.S Patents and Applications, such as U. S. Patent Nos. 5,763,548; 5,807,937; 5,789,487; 5,945,491; 6,111,022; 6,121,371; 6,124,411; 6,162,882; 6,407,187; 6,512,060; 6,538,091; 6,541,580; 6,624,262; 6,624,263; 6,627,314; 6,759,491; and U.S. Patent Applications 09/534,827; 09/972,056; 10/034,908; 10/269,556; 10/289,545; 10/638,584; 10/860,807; 10/684,137; 10/781,061 and 10/992,249, all of which are herein incorporated by reference to provide examples of active transition metal complexes and ATRP initiators. ATRP has also been discussed in numerous publications with Matyjaszewski as co-author and reviewed in several book chapters. [*ACS Symp. Ser.,* **1998**, *685*; *ACS Symp. Ser.,* **2000**; *768; Chem. Rev.* **2001**, *101*, 2921-2990; *ACS Symp. Ser.,* **2003**; *854.]*. Similar polymerization processes comprising the similar of reagents may be referred to by different names, such as transition metal mediated polymerization or atom transfer polymerization, but the processes are considered to be identical and are referred to herein as "ATRP".

US Patent 6,569,967 (WO 00/49027) concerns formation of alkoxyamines derived from β-phosphorous nitroxides wherein the preferred process used to prepare the compounds is the method involves the ATRA or ATRC reaction disclosed in WO 98/07758. A transition metal catalyst comprising bipyridine (bpy) was employed in WO 98/07758 for the formation of alkoxyamines from nitroxides, such as TEMPO, and alkyl halides.

In United States Patent No. 6,657,043 (WO 00/71501), a reaction is described with molecules comprising multiple halides thereby providing multi-functional β-substituted nitroxide initiators for nitroxide mediated polymerization. Such multifunction β-substituted nitroxide initiators may be used in a nitroxide mediated polymerization that would result in star and/or graft copolymers. The patent describes the coupling of a carbon-based radical with a nitroxide radical. The coupling reaction was described as proceeding by activating a halo derivative $R(X)_n$ in the presence of an organometallic system, for instance CuX/ligand

(X=Cl or Br) according to a reaction of ATRA as described by D. Greszta et al. in Macromolecules *1996*, 29, 7661-7670 and WO 98/07758.

In United States Patent No. 6,700,007 a method for preparing alkoxyamines from nitroxides in the presence of ionic liquids was disclosed. The ionic liquid is employed to assist in separation of the copper complex from the reaction media. However, copper zero is the agent added to the reaction to drive the ATRA or ATRC reaction to completion. The use of ionic liquids to assist in separation of copper from an ATRP reaction has been discussed in Carmichael, A. J.; et.al *Chem. Commun.* **2000**, 1237-1238, and was amplified in Sarbu, T.; Matyjaszewski, K. published in *Macromolecular Chemistry and Physics* **2001**, *202*, 3379-3391.

Reducing agents have been employed to reduce the concentration of the deactivator, or persistent radical, in an ATRP process thereby increasing the rate of reaction. Without a reducing agent, an ATRP process may slow down as the concentration of activator decreases and the deactivator increases due to termination reactions. The ATRP process will stop if all activator is converted to deactivator. Reducing agents were added to the reaction medium at low concentrations compared to the mole fraction of R-X initiators. Sugars have been known as reducing agents for cupric salts, [Cramer, W. *Proc. Chem. Soc.* **1914**, *30*, 293]; and various reducing monosaccharides have an effect on the rate of an ATRP of butyl methacrylate. See de Vries, A.; Klumperman, B.; de Wet-Roos, D.; Sanderson, R. D. *Macromol. Chem. Phys.* **2001**, *202*, 1645-1648, hereby incorporated by reference in its entirety. The addition of reducing sugars was shown to affect the rate of polymerization in an ATRP, with a 100% increase in the rate of polymerization was realized in some cases. A possible explanation for these observations is the ability of the reducing sugars to reduce part of the transition metal complex in the higher oxidation state, for example $Cu^{(II)}$ which deactivate the growing radicals, to transition metal complex in the lower oxidation state, $Cu^{(I)}$, thereby inducing a shift in the equilibrium between active and dormant chains in the direction of the former with a resulting increase in the rate of reaction. Complete reduction of the $Cu^{(II)}$ species in a controlled ATRP reaction is not desired. Such sugars do not significantly interact with the catalyst, do not form side products (complexes) with it and the reducing activity is at least partially decreased by the low solubility of the sugars in the reaction medium. Therefore, these sugars were successful at increasing the propagation rate while not totally reducing the catalyst, thus, retaining control over the reaction. The sugars were added to the ATRP in sub-stoichiometric amounts.

U.S. Patent 6,310,149 describes an increase in polymerization rate noted when phenols are added to an ATRP process. Phenols may act to reduce $Cu^{(II)}$ species and initiate reverse ATRP. See Gnanou et al., *Journal of Polymer Science, Part A: Polymer Chemistry* **2004**, *42*, 351-359, hereby incorporated by reference in its entirety. However, when a macroinitiator was used as the ATRP initiator in the reverse ATRP activated by phenol, the polymer displayed a bimodal molecular weight distribution and it was concluded there may have been side reactions resulting in the formation of a low molecular weight peak. No mechanism was proposed for the results, and it is possible that the low molecular weight peak is due to polymerization from phenoxy radicals in the system. The phenols were added to the ATRP in sub-stoichiometric amounts.

The addition of octanethiol, a free-radical chain transfer agent, also caused an increase in the rate of an ATRP process. The octanethiol may have caused a reduction in the concentration of $Cu^{(II)}$ as a result of the oxidation of the thiol to a disulfide. See Heuts, J. P. A. *et. al. Macromol. Chem. Phys.* **1999**, *200*, 1380-1385, hereby incorporated by reference in its entirety. The thiols were added to the ATRP in sub-stoichiometric amounts.

Further processes for increasing the rate of ATRP processes are the addition of Lewis acids, metal halides, acetyl acetonate and other organic acids, such as camphorsulfonic acid. Preferred Lewis acids include aluminium complex compounds, metal halides, e. g. zinc halides, lithium halides, iron trichloride, boron trifluoride. A preferred aluminium compound is methyl aluminium bis(2,6-di-tert-butyl-4-methyl) phenoxide. No mechanism was suggested for the increased rate and there was no suggestion that the reactions could be used to activate a reverse ATRP. See WO 00/47634, hereby incorporated by reference.

The cited patents and patent applications are incorporated by reference into this application to provide examples of the range of nitroxides that can be converted into alkoxyamines by a controlled redox transfer reaction comprising a transition metal in its lower oxidation state to activate an ATRP initiator forming a radical that can couple with the added nitroxide.

The alkoxyamines produced by such processes are suitable for the preparation of macromolecules with controlled topology, composition and functionality by nitroxide mediated polymerization processes, (NMP).

Therefore, there is a need for a process for the preparation of alkoxyamines from a broad spectrum of nitroxides or nitroxide precursors. There is a need for a process that provides alkoxyamines for a reduced cost and a reduced environmental impact.

SUMMARY OF INVENTION

The invention relates to an improved method for conducting an atom transfer radical addition ("ATRA") reaction or an atom transfer radical coupling ("ATRC") reaction. In ATRC or ATRA reactions, a radical is formed and, typically, reacted with a vinyl compound to form a product. One embodiment of this invention is directed to a process for the preparation of alkoxyamines, the process comprises reacting an ATRP initiator and a nitroxide in the presence of a reaction medium comprising a reducing agent and at least one transition metal catalyst. Any compound that may act as an ATRP initiator is capable of being used in this coupling reaction. The inventors believe that the transition metal catalyst homolytically cleaves the radically transferable atom or group from the ATRP initiator to form a radical. The addition of the radically transferable atom or group to the transition metal catalyst results in an increase in its oxidation state. Typically, the transition metal in the higher oxidation state would not be able to initiate formation of an additional radical, that is it is a stoichiometric reaction. Therefore, an equal molar ratio of transition metal to ATRP initiator is typically required. The molar ratio may be decreased if the a substantial portion of the transition metal is in its zero oxidation state and may participate in a redox reaction with an initiator compound twice, in the first reaction forming $Cu^{(I)}$ and in the second $Cu^{(II)}$. The reducing agent in the reaction medium, however, allows significantly lower concentrations of transition metal to be present and significantly lower ratios of transition metal to ATRP initiator to be present in the reaction medium and still drive the reaction to completion. The molar ratio of the transition metal to the ATRP initiator may be less than 0.5, or less than 0.1, or even less than 0.05. There may be process, cost, and environmental advantages to operating the process with low amounts of the transition metal catalyst. In a further embodiment, the transition metal catalyst may be in an oxidized state and the process of the invention may comprise reacting the reducing agent with at least one of the transition metal catalyst in an oxidized state and an ATRP initiator. Reduction of the transition metal catalyst in the higher oxidation state will result in formation of the activator form of the catalyst.

In another embodiment, the invention is directed to a process comprising coupling an ATRP initiator and a stable free radical in the presence a reaction medium comprising at least one transition metal catalyst and a reducing agent. The molar ratio of the transition metal to the ATRP initiator may be less than 0.5, or less than 0.25, or in certain embodiments less than 0.01.

Embodiments of the invention are further directed to an atom transfer radical addition or coupling reaction process comprising an organic reducing agent. In another

embodiment, the preparation of alkoxyamines from nitroxides comprises conducting an atom transfer addition reaction or an atom transfer coupling reaction, wherein an ATRP initiator is activated by a catalytic amount of a transition metal complex in its lower oxidation state. The ATRP initiator interacts with the transition metal complex to form an active radical species that may react with a stable free radical molecule. The stable free radical may be added or generated in the reaction system.

The reaction may be driven to completion by a second reaction wherein the transition metal complex in the higher oxidation state is reduced to its activator state by reaction with a reducing agent.

The stable free radical may be formed in a redox reaction with the transition metal catalyst complex in the higher oxidation state. Such a reaction forms the stable free radical and the transition metal complex in the lower oxidation state. This reaction scheme allows the active transition metal complex to be regenerated and, therefore, to be present in sub-stoichiometric concentrations compared to the concentration of radically transferable atoms or groups, or nitroxide precursors in the reaction medium. The transition metal complex and reducing agent thereby act as a catalyst for the coupling reaction by continuously forming the radical that reacts with the stable free radical.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1C illustrate reaction schemes of embodiments of the invention for the production of an alkoxyamine, Figure 1A illustrates a reaction scheme of an embodiment comprising a stable free radical nitroxide added to the reaction medium, Figure 1B illustrates a reaction scheme of an embodiment comprising a nitroxide prepared from an nitroxide precursor, Figure 1C illustrates a reaction scheme of an embodiment of a process for the preparation of an alkoxyamine from R-X, a dormant initiator species, and TEMPO, an stable free radical nitroxide;

Figure 2 illustrates the reaction scheme of an embodiment of a process comprising activating a dormant initiator by a transition metal complex in the lower oxidation state to form a radical that couples with a nitroxide to form an alkoxyamine with continuous regeneration of the transition metal in the lower oxidation state by reaction with a reducing agent;

Figure 3 illustrates the reaction scheme for reduction of $Cu^{(II)}$ to $Cu^{(I)}$ by $tin^{(II)}$ 2-ethlhexanoate;

Figure 4 is a graph of the activation rate constants for copper complexes formed with various ligands with EtBriB as initiator in the presence of $Cu^{I}X$ (X = Br or Cl) in MeCN at 35 °C.; and

Figures 5A-5C are graphs of the GPC traces from click chemistry reactions of diazido polystyrene with propargyl ether using CuBr/Me_6TREN as catalyst in reduced concentrations under limited air with hydrazine (Figure 5A), without hydrazine (Figure 5B), and with a large excess of hydrazine (Figure 5C) after 0.5 hour, 1 hour, 3 hours, 6 hours, 24 hours, and 48 hours.

DETAILED DESCRIPTION

The invention relates to an improved method for conducting an atom transfer radical addition ("ATRA") reaction or an atom transfer radical coupling ("ATRA") reaction. In ATRC or ATRA reactions, a radical is formed and, typically, reacted with a vinyl compound to form a product. One embodiment of this invention is directed to a process for the preparation of alkoxyamines, the process comprises reacting an ATRP initiator and a nitroxide in the presence of a reaction medium comprising a reducing agent and at least one transition metal catalyst. Any compound that may act as an ATRP initiator is capable of being used in this coupling reaction. The inventors believe that the transition metal catalyst homolytically cleaves the radically transferable atom or group from the ATRP initiator to form a radical. The addition of the radically transferable atom or group to the transition metal catalyst results in an increase in its oxidation state. Typically, the transition metal in the higher oxidation state would not be able to initiate formation of an additional radical by further reaction with an ATRP initiator. Therefore, an equal molar ratio of transition metal to ATRP initiator is typically required. The molar ratio may be decreased if a substantial portion of the transition metal is in its zero oxidation state and may react with an ATRP initiator compound twice, initially forming $Cu^{(I)}$ then $Cu^{(II)}$.

The presence of the reducing agent in the reaction medium, however, allows significantly lower concentrations of transition metal catalyst and significantly lower ratios of transition metal catalyst to ATRP initiator to be present in the reaction medium and still drive the reaction to completion. The molar ratio of the transition metal to the ATRP initiator may be less than 0.5, or less than 0.1, or even 0.05 or most preferably less than 0.01. Embodiments of processes of the invention may comprise a concentration of transition metal catalyst in the reaction medium of less than 1000 ppm, or even less than 100 ppm, and in certain embodiments, the concentration of transition metal catalyst in the reaction medium

may be less than 50 ppm. The addition of a base, or excess ligand, to the reaction medium may assist in the coupling reaction and/or reduction reaction.

There may be process, cost, and environmental advantages to operating the process with low amounts of the transition metal catalyst. In a further embodiment, the transition metal catalyst may be in an oxidized state and the process of the invention may comprise reacting the reducing agent with at least one of the transition metal catalyst in an oxidized state and an ATRP initiator. Reduction of the transition metal catalyst in the higher oxidation state will result in formation of the activator form of the catalyst. Embodiments of the present invention include methods of preparing alkoxyamines. In certain embodiments, the processes of the invention may be considered to comprise an ATRC or an ATRA reaction to convert a nitroxide to an alkoxyamine. In one embodiment of the invention the process comprises a transition metal complex in a lower oxidation state (M^+Y/L_n). An ATRP initiator ($R\text{-}X_n$) homolytically transfers at least one radically transferable atom or group (X) in a redox reaction to form the transition metal complex in the higher oxidation state ($X\text{-}Mt^{n+1}Y/L_n$) and a radical species (R^*). The transition metal complex in the higher oxidation state may comprise the radically transferable atom or group (X) as a ligand or counterion. The radical species may then react with a nitroxide ($R^1R^2N\text{-}O^*$) to form an alkoxyamine ($R^1R^2N\text{-}O\text{-}R$).

The transition metal complex in the higher oxidation state will, in most cases, be unable to further activate another compound ($R\text{-}X_n$) comprising a radically transferable atom or group. However, the transition metal complex in the higher oxidation state, ($X\text{-}Mt^{n+}Y/L_n$), may then be reduced to the lower oxidation state, (M^+Y/L_n), by a reaction with a reducing agent in a reduction reaction, in certain embodiments, such a reaction does not form a radical species. An embodiment of such a reduction reaction is shown in Figure 3. In Figure 2, a copper based catalyst complex interacts with a mono-functional macroinitiator comprising a halide as the radically transferable atom.

Figure 1A illustrates a reaction scheme of an embodiment comprising reacting an ATRP initiator (RX) and a nitroxide ($O\text{-}NR_1R_2$) in the presence of a reaction medium comprising a reducing agent and at least one transition metal catalyst (M_t^+) in a lower oxidation state. The transition metal complex is involved in a redox reaction with the compound (RX) to form a radical that reacts with the stable free radical nitroxide ($^*ONR_1R_2$) to form an alkoxyamine ($RONR_1R_2$) and a transition metal complex in the higher oxidation state ($M_t^{++}X$). A reducing agent then reduces the transition metal complex in the higher oxidation state to a transition metal complex in the lower oxidation state. In such an

embodiment, the molar ratio of the transition metal to the ATRP initiator may be less than 0.5. Figure 1B illustrates another embodiment of the process of the invention comprising an additional reaction converts a nitroxide precursor, such as $HONR_1R_2$ to a nitroxide ($*ONR_1R_2$). The nitroxide prepared from the nitroxide precursor may then react to with the radical to form the alkoxyamine. Figure 1C illustrates a reaction scheme of a more specific embodiment of a process for the preparation of an alkoxyamine from R-X, a dormant initiator species, and TEMPO, a stable free radical nitroxide.

The invention is also exemplified by the reaction scheme shown in Figure 1B by the oxidation/reduction reaction of 1-hydroxy-2,2,6,6-tetramethyl-piperidine/TEMPO with copper complexes can be used in a catalytic cycle to form alkoxyamines.

In the first step of the reaction scheme of Figure 1B, 1-hydroxy-2,2,6,6-tetramethyl-piperidine is oxidized to TEMPO by a Cu(II) complex forming a Cu(I) complex. The Cu(I) complex may then remove a radically transferable atom or group from an ATRP initiator in a reduction reaction forming a radical that can couple with the nitroxide, TEMPO. The Cu(II) complex can oxidize a further molecule of 1-hydroxy-2,2,6,6-tetramethyl-piperidine to TEMPO continuing the reaction in a forward direction. This reaction is applicable to any nitroxide precursor in the presence of a suitable catalyst complex.

Figure 2 illustrates a reaction scheme of an embodiment of a process comprising activating an ATRP initiator that is a polymeric initiator or a initiator attached to a particle or a substrate (Pn-X) by a transition metal complex in the lower oxidation state to form a radical that couples with a nitroxide to form an alkoxyamine. The reaction scheme of Figure 2 also illustrates the continuous regeneration of the transition metal in the lower oxidation state by reaction with a reducing agent.

Embodiments of the process of the invention may comprise a reducing agent that can reduce the transition metal complex in an oxidized state to an lower oxidized state and convert the reducing agent to an oxidized agent. The reducing agent should not form an oxidized agent that can itself or form another species that can either interact with the catalyst complex or interact with the stable free radical nitroxide. Reducing agents that conduct the reduction reaction, essentially without formation of radicals capable of interacting with any reagent present in the reaction medium are preferred. Stanous 2-ethylhexanoate, ($Sn(2EH)_2$) is one of many possible reducing agents that may be used in embodiments of the present invention. $Sn(2EH)_2$ can reduce $Cu^{(II)}$ to $Cu^{(I)}$ (See Figure 3) in a non-radical forming reduction reaction.

Further, embodiments may comprise reducing agents that are more environmentally benign than the transition metals. None of the previous reactions wherein reducing agents are added to an ATRP to increase the rate suggest that the reducing agents may be used to reduce the molar ratio of the transition metal catalyst to the atom transfer radical polymerization initiator nor that the reducing agents be suitable for other reactions involving atom transfer from an ATRP initiator. The reducing power of different transition metal complexes are known [Lingane, J. J., *Chem. Rev.*; **29** 1 1941: Vlcek, A. A., *Coord. Chem. Rev.* **43** 39, 1982; van Gaal, H. M. L., van der Linden, J. G. M., *Coord. Chem. Rev.* **47** 41 1982] and one only has to chose a complex that can reduce the transition metal complex selected as the catalyst for the ATRC reaction, preferably, without further significant participation in the reaction process. Different transition metal complexes may be reduced to a different degree by the same reagent. The reducing agent may undergo a dehydrohalogenation reaction after oxidation. The addition of a base or excess ligand may accelerate some reduction reactions particularly when the reduction reaction involves direct or indirect formation of an acid species. The base may be in the form of additional N-containing ligand, for example.

The activity of the reducing agent can however be controlled by selecting a reducing agent that is only slightly soluble in the reaction medium. The slow dissolution of the agent in the reaction medium maintains a low concentration of the reducing agent in the reaction that controllably drives the reaction forward while reducing the tendency of unwanted radical-first radical coupling reactions. Paleos [Paleos, C. M.; Dais, P. *Journal of the Chemical Society, Chemical Communications* **1977**, 345-346] discussed the ready reduction of some nitroxide free radicals with ascorbic acid, but use of a solvent in which ascorbic acid or one of its derivatives has poor solubility allows slow controlled abstraction of the halide generating a radical for capture rather than reduction of the nitroxide. The low concentration of reducing agent in solution with the reactants minimizes the interaction of the stable free radical and the reducing agent. In some embodiments, the reaction will not proceed forward if the concentration of reducing agent is too high. The concentration of the reducing agent may be controlled by continuously or intermittently adding a small amount of reducing agent or by utilizing a reducing agent with a low solubility in the other components of the reaction medium. The low solubility of the reducing agent limits the concentration of the reducing agent in the phase that comprises the stable free radical or the nitroxide. It is believed that the low concentration of a strong reducing agent limits any interaction between the reducing agent and the stable free radical or nitroxide that would inhibit or prevent the

coupling reaction from occurring. The solubility of the reducing agent should be such that the concentration of the reducing agent in the phase of the reaction medium that comprises the stable free radical or the nitroxide is less than 5 wt.% or less than 1wt.%for a reducing agent with a high reducing activity, less than 1000 ppm or less than 500 ppm, or even less than 100 ppm for even more active reducing agents. For example, the continuous presence of ascorbic acid in concentrations of less than 100 ppm or even 50 ppm is sufficient to reduce the transition metal complex from an oxidized state to an activator state in anisole solvent. At this concentration, ascorbic acid doesn't interact with the stable free radical but still performs the required reduction of the of the transition metal catalyst. The ascorbic acid may remain as a solid in the reaction medium and then be solubilized as the soluble ascorbic acid is converted to dehydroascorbic acid. The phase of the reaction that comprises the stable free radical or the nitroxide is the phase that comprises a substantial portion of the stable free radical or nitroxide. The phase need not, but may, comprise all of the stable free radical or nitroxide.

Though the mechanism of inhibition of the reaction is not known in the presence of an active reducing agent, it is speculated that if too much of an active reducing agent is present in the reaction medium, the stable free radical or nitroxide may be reduced to a non-reactive form. For instance, the nitroxide may be reduced by loss of oxygen to a more stable form. Conversely, a second mechanism in which the reducing agent donates hydrogen to the nitroxide may result in a non-reactive species. The concentration of the reducing agent in the phase of the reaction medium that comprises the stable free radical of the nitroxide should be balanced with the activity of the reducing agent, specifically the activity of the reducing agent to interact with the other reactants to inhibit the reaction.
The concentration of the reducing agent in the phase of the reaction medium that comprises the stable free radical of the nitroxide may also be controlled by the addition rate of the reducing agent to the reaction medium. A more soluble reducing agent may be added in such a manner to maintain the desired concentrations of reducing agent as described above.

The reducing agent may be soluble in the reaction medium or in at least one phase of the reaction medium, such as the suspending phase or the organic phase for reaction processes having at least two phases. In typical multiphase reaction processes, the reaction medium may include water. Preferably, reducing agent will be at least partially soluble in the desired phase of the reaction medium, have a reducing rate to substantially maintain the desired ratio of transition metal in the lower oxidation state to the higher oxidation state. The addition of a base or excess ligand to any phase of the reaction medium may assist in

increasing the concentration of the transition metal catalyst allowing extraction of the radically transferable atom or group from the ATRP initiator.

The reducing agent may be added to a higher oxidation state catalyst complex forming an active catalyst complex, possibly by an outer sphere electron transfer reaction or by formation of the activator through a lower energy transition state complex that does not result in full separation of intermediate species which could result in formation of independent activating species.

In certain embodiments, the reducing agent may be considered to be a trap for the radically transferable atoms or groups. As used herein, a trap for the radically transferable atoms or groups is any compound can trap the radically transferable atom or group to prevent the radically transferable atom or group, exemplified by a halogen, from further participation in the activation process or the deactivation process. For instance, to initiate the coupling process, the halogen trap may reduce the transition metal compound in a higher oxidation state to a transition metal compound in the lower oxidation state.

In another embodiment of the invention the reducing agent employed to reduce a transition metal complex in the higher oxidation state is a precursor to the stable free radical. This is herein exemplified by the addition of a nitroxide precursor such as 1-hydroxy-2,2,6,6-tetramethyl-piperidine to a reaction medium further comprising copper complexes and an ATRP initiator. The transition metal complexes participate in a dual redox reaction forming both reactive molecules. The higher oxidation state transition metal complex participates in a redox reaction with 1-hydroxy-2,2,6,6-tetramethyl-piperidine forming TEMPO and a Cu(I) complex which abstracts a halogen atom from an ATRP initiator forming a radical to couple with the stable free radical and a Cu(II) complex thereby completing one redox cycle for the transition metal complex.

All catalyst complexes suitable for ATRP will be suitable in embodiments of the process of the invention. The ligand of the catalyst complex affects the activation rate constants and the solubility of the transition metal complex in the reaction medium. The activity of transition metal complexes comprising specific exemplary ligands for a specific ATRP initiator, ethyl 2-bromoisobutyrate, is shown in Figure 4.

Therefore, a catalyst complex with a suitable ligand may be selected to provide a suitable reaction rate for the targeted coupling reaction. A preferred transition metal complex would result in a process comprising a minimum of R^* / R^* coupling and, therefore predominantly all R^*'s are captured by the stable free radical. Suitable complexes include: $CuCl_2$/dNbpy, $CuCl_2$/PMDETA, $CuBr_2$/PMDETA, $CuCl_2$/Me_6TREN or preferentially for

formation of alkoxyamines CuX_2/Cyclam since that particular complex is a very efficient activator but poor deactivator. Unlike an ATRP, where deactivation of the growing radical is important, deactivation is undesirable for an ATRC or ATRA. Use of such an active activator allows use of lower levels of catalyst in the addition reaction. However, for other ATRA reactions with less robust capturing molecules slower generation of the radicals from the ATRP initiator may be preferred thereby demonstrating the broad applicability of embodiments of the atom transfer process for the present invention.

The reduction reaction or the ATRP initiator may be preferentially conducted in-situ or, optionally, if desired, prior to addition of the catalyst complex to the reaction medium. Appropriate conditions can be determined by examining the kinetics of the reduction reaction for the transition metal chemistry, as noted below, or validated by running a reaction using a monofunctional macroinitiator followed by GPC analysis of the product. In a preferred embodiment, the rate of formation of the radical from the ATRP initiator should be such that minimal direct radical/ radical coupling occurs and most, or predominantly all, radicals formed from the ATRP initiator are captured by the stable free radical or added olefin to form the desired product. This procedure has all the benefits of a normal ATRC initiated reaction plus the benefits, or freedom, of adding the catalyst complex to the reaction medium in its more stable higher oxidation state, in the presence of the initiator (R-X), and, optionally, in the presence of dissolved oxygen. In some cases, the ATRP initiator may be attached to a surface.

Since the activator is continuously regenerated by a reducing agent, the rate of the initiation of the coupling reactions can be tuned by the addition rate, amount, or composition of the reducing agent. In this way, the rate of the ATRC can be constantly controlled throughout the coupling process by adjusting, for example, the $Cu^{(I)}/Cu^{(II)}$ ratio with the continuous or intermittent addition of the reducing agent.

In one embodiment of the invention, the reducing agent may be poorly soluble in the reaction medium. In such an embodiment, the rate of slow dissolution of the reducing agent moderates the rate of the reduction reaction. Indeed, if the solubility of the reducing agent is very low, the rate of the reduction reaction may be moderated by the rate of the heterogeneous reaction of the Cu(II) complex with the solid surface of the reducing agent.

In certain embodiments, the level of transition metal complex may be so low that the reaction medium may appear colorless and the transition metal complex can either be left in the final product or, since it is added at such low levels it can be inexpensively and readily removed from the reaction at the end of the reaction by filtration over an active

substrate or extraction into a solvent, such as, water in some embodiments. Further, since the transition metal may be removed as the higher oxidation state complex, i.e. after exposure to air, it is an ideal component for recycle into the process as the catalyst precursor.

In certain embodiments, the amount of reducing agent added should be sufficient to reduce most of the transition metal complex is a higher oxidation state to its lower oxidation state, remove any excess oxygen from the system, and continue to reduce the transition metal in the higher oxidation state formed as a result of the activation reactions, in some cases, at a similar rate to formation of the transition metal in the higher oxidation state. Thus, a further aspect of the invention is that oxygen does not have to be removed from the reaction medium prior to adding the reducing agent and initiating the coupling process. The reducing agent can continuously reduce the higher oxidation state transition metal complex so that it additionally interacts with the dissolved oxygen and removes it from the process. In some processes, however, it may be desirable to limit the dissolved oxygen in the reaction medium.

Embodiments of the present invention include reducing agents that reduce the transition metal catalyst in the oxidized state, and when the higher oxidation state comprises radically transferable atoms or groups as a ligand or counterion by removal of a radically transferable atom or group, typically a halogen. Typically the reducing agent is such that it prevents the radically transferable atom or group from further participating in activation processes. The reducing agent may prevent the radically transferable atom or group from further participating in the coupling process by oxidation of the reducing agent to a more stable higher oxidation state or by reaction with a halogen to form a halogen-containing compound that will not further participate in the process as a reactant, or by undergoing a dehydrohalogenation reaction, for example. The reducing agent may be an inorganic compound or an organic compound comprising reducing capability.

Suitable reducing agents such as sugars are known in the art [Cramer, W. *Proc. Chem. Soc.* **1914**, *30*, 293. Levine, V. E.; Merlis, S. *Bull. Creighton Univ. School Med.* **1947**, *4*, 14-15. Reiner, M.; Preiss, J. *Baskerville Chemical Journal* **1953**, *4*, 15-17. Singh, M. P.; Ghosh, S. *Zeitschrift fuer Physikalische Chemie (Leipzig)* **1957**, *207*, 198-204.] and exemplified in commonly assigned patent applications PCT/US05/007265 and US Provisional Application 60/711,722.

Ascorbic acid is a suitable reducing agent; it has been found to reduce transition metals that are suitable as ATRP catalyst, in particular iron, even in the presence of oxygen, see Samuni, A. *et. al. European journal of Biochemistry; 1983, 137*, 119-124 and

Davies, M. B. *Polyhedron* **1992**, *11*, 285-321 both papers are hereby incorporated by reference in their entirety. These papers discuss the reducing effect on transition metals. Ascorbic acid which is an active reducing agent in an aqueous solution but the rate of the reduction reaction can be moderated by conducting the reaction in non-polar solvents in which the ascorbic acid is less soluble.

Further, suitable reducing agents for the present invention may be, for example, ascorbic acid, ascorbic acid-6-palmitaite (A6P), stannous compounds, stannous oxalate, sodium sulfite, sulfur compounds of a low oxidation state, sodium hydrogen sulfite, inorganic salts comprising a metal ion, hydrazine hydrate, alkylthiols, mercaptoethanol, carbonyl compounds which can easily be enolized, acetyl acetonate, camphorsulfonic acid, hydroxy-acetone, reducing sugars, monosaccharides, glucose and related sugars, tetrahydrofuran, dihydroanthracene, silanes, 2,3 dimethylbutadiene, amines, polyamines, hydrazine derivatives, formamidinesulfinic acid, silane compounds, borane compounds, aldehydes, and derivatives of such compounds. The metal ions of the inorganic salts may be, for example, at least one of Sn^{2+}, Fe^{2+}, Cr^{3+}, Al^{3+}, Ti^{3+} and Ti^{4+} and, preferably, in certain embodiments, the metal ion may be at least one of Sn^{2+}, Fe^{2+}, Cr^{3+} and Ti^{3+}. In certain embodiments, the reducing agent may preferably be capable of reacting with oxygen, or reducing a transition metal catalyst that has been oxidized by oxygen such as dissolved oxygen in the reaction medium.

Suitable reducing agents may also be antioxidants and the following list of *antioxidants* provides a further selection of reducing agents. Antioxidants suitable as reducing agents, include but are not limited to, alkylated monophenols, for example 2,6-di-tert-butyl-4-methylphenol, 2-butyl-4,6-di-methylphenol, 2,6-di-tert-butyl-4-ethylphenol, 2,6-di-tert-butyl-4-n-butylphenol, 2,6-di-tert-butyl-4-isobutylphenol, 2,6-dicyclopentyl-4-methylphenol, 2-(.alpha.-methylcyclohexyl)-4,6-di-methylphenol, 2,6-dioctadecyl-4-methylphenol, 2,4,6-tricyclohexylphenol, 2,6-di-tert-butyl-4-methoxymethylphenol, linear nonylphenols or nonylphenols branched in the side-chain, e.g. 2,6-dinonyl-methylphenol, 2,4-dimethyl-6-(1'-methylundec-1'-yl)-phenol, 2,4-dimethyl(1'-methylheptadec-1'-yl)-phenol, 2,4-dimethyl-6-(1'-methyltridec-1'-yl)-phenol and derivatives thereof;alkylthiomethylphenols, for example 2,4-dioctylthiomethyl-6-tert-butylphenol, 2,4-dioctyl-thiomethyl-6-methylphenol, 2,4-dioctylthiomethyl-6-ethylphenol, 2,6-didodecylthiomethyl-4-nonylphenol, and derivatives thereof; hydroquinones and alkylated hydroquinones, for example 2,6-di-tert-butyl-4-methoxy-phenol, 2,5-di-tert-butylhydroquinone, 2,5-di-tert-amylhydroquinone, 2,6-diphenyl-4-octa-decyloxyphenol, 2,6-di-tert-butylhydroquinone, 2,5-di-tert-butyl-4-

hydroxyanisole, 3,5-di-tert-butyl-4-hydroxyanisole, 3,5-di-tert-butyl-4-hydroxyphenyl stearate, bis(3,5-di-tert-butyl-4-hydroxyphenyl) adipate, and derivatives thereof; tocopherols, for example .á.-tocopherol, .β.-tocopherol, .γ.-tocopherol, .δ.-tocopherol and derivativesthereof (Vitamin E); hydroxylated thiodiphenyl ethers, for example 2,2'-thiobis(6-tert-butyl-4-methylphenol), 2,2'-thiobis(4-octylphenol), 4,4'-thiobis(6-tert-butyl-3-methylphenol), 4,4'-thiobis(6-tert-butyl-2-methylphenol), 4,4'-thiobis(3,6-di-sec-amylphenol), 4,4'-bis(2,6-dimethyl-4-hydroxyphenyl) disulfide; and derivatives thereof; alkylidene bisphenols, for example 2,2'-methylenebis(6-tert-butyl-4-methylphenol), 2,2'-methylenebis(6-tert-butyl-4-ethylphenol), 2,2'-methylenebis[4-methyl-6-(.alpha.-methylcyclohexyl)-phenol], 2,2'-methylenebis(4-methyl-6-cyclohexylphenol), 2,2'-methylenebis(6-nonyl-4-methylphenol), 2,2'-methylenebis(4,6-di-tert-butylphenol), 2,2'-ethylidenebis(4,6-di-tert-butyl-phenol), 2,2'-ethylidenebis(6-tert-butyl-4-isobutylphenol), 2,2'-methylenebis[6-(.alpha.-methylbenzyl)-4-nonylphenol], 2,2'-methylenebis[6-(.alpha.,.alpha.-dimethylbenzyl)-4-nonylphenol], 4,4'-methylenebis(2,6-di-tert-butylphenol), 4,4'-methylenebis(6-tert-butyl-2-methylphenol), 1,1-bis(5-tert-butyl-4-hydroxy-2-methylphenyl)butane, 2,6-bis(3-tert-butyl-5-methyl-2-hydroxybenzyl)-4-methylphenol, 1,1,3-tris(5-tert-butyl-4-hydroxy-2-methylphenyl)butane, 1,1-bis(5-tert-butyl-4-hydroxy-2-methylphenyl)-3-n-dodecylmercaptobutane, ethylene glycol bis[3,3-bis(3'-tert-butyl-4'-hydroxyphenyl)butyrate], bis(3-tert-butyl-4-hydroxy-5-methylphenyl)dicyclopentadiene, bis[2-(3'-tert-butyl-2'-hydroxy-5'-methylbenzyl)-6-tert-butyl-4-methylphe- nyl]terephthalate, 1,1-bis(3,5-dimethyl-2-hydroxyphenyl)butane, 2,2-bis(3,5-di-tert-butyl-4-hydroxyphenyl)propane, 2,2-bis(5-tert-butyl-4-hydroxy-2-methylphenyl)-4-n-dodecylmercaptobutane, 1,1,5,5-tetra(5-tert-butyl-4-hydroxy-2-methylphenyl)pentane, and derivatives thereof; O- , N- and S-benzyl compounds, for example 3,5,3',5'-tetra-tert-butyl-4,4'-dihydroxy-dibenzyl ether, octadecyl-4-hydroxy-3,5-dimethylbenzyl mercaptoacetate, tridecyl-4-hydroxy-3,5-di-tert-butylbenzyl mercaptoacetate, tris(3,5-di-tert-butyl-4-hydroxybenzyl)amine, bis(4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl) dithioterephthalate, bis(3,5-di-tert-butyl-4-hydroxy-benzyl) sulfide, isooctyl-3,5-di-tert-butyl-4-hydroxybenzyl mercaptoacetate, and derivatives thereof; hydroxybenzylated malonates, for example dioctadecyl 2,2-bis(3,5-di-tert-butyl-2-hydroxybenzyl)malonate, dioctadecyl 2-(3-tert-butyl-4-hydroxy-5-methylbenzyl)malonate, didodecylmercaptoethyl 2,2-bis(3,5-di-tert-butyl-4-hydroxybenzyl)malonate, di-[4-(1,1,3,3-tetramethylbutyl)phenyl]2,2-bis(3,5-di-tert-butyl-4-hydrox- ybenzyl)malonate, and derivatives thereof; hydroxybenzyl aromatic compounds, for example 1,3,5-tris(3,5-di-tert-butyl-4-hydroxy-benzyl)-2,4,6-trimethylbenzene, 1,4-bis(3,5-

di-tert-butyl-4-hydroxybenzyl)-2,3,5,6-tetra-methylbenzene, 2,4,6-tris(3,5-di-tert-butyl 4-hydroxybenzyl)phenol, and derivatives thereof; triazine compounds, for example 2,4-bisoctylmercapto-6-(3,5-di-tert-butyl-4-hydroxy-anilino)-1,3,5-triazi- ne, 2-octylmercapto-4,6-bis(3,5-di-tert-butyl-4-hydroxyanilino)-1,3,5-tri– azine, 2-octylmercapto-4,6-bis(3,5-di-tert-butyl-4-hydroxyphenoxy)-1,3,5-t- riazine, 2,4,6-tris-(3,5-di-tert-butyl-4-hydroxyphenoxy)-1,2,3-triazine, 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl) isocyanurate, 1,3,5-tris(4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl)isocyanurate, 2,4,6-tris(3,5-di-tert-butyl-4-hydroxyphenylethyl)-1,3,5-triazine, 1,3,5-tris(3,5-di-tert-butyl-4-hydroxyphenylpropionyl)hexahydro-1,3,5-tri- azine, 1,3,5-tris(3,5-dicyclohexyl-4-hydroxybenzyl) isocyanurate, and derivatives thereof; benzylphosphonates, for example dimethyl 2,5-di-tert-butyl-4-hydroxybenzylphosphonate, diethyl 3,5-di-tert-butyl-4-hydroxybenzylphosphonate, dioctadecyl 3,5-di-tert-butyl-4-hydroxybenzylphosphonate, dioctadecyl 5-tert-butyl-4-hydroxy-3-methylbenzyl-phosphonate, calcium salt of 3,5-di-tert-butyl-4-hydroxybenzyl-phosphonic acid monoethyl ester, and derivatives thereof; acylaminophenols, for example 4-hydroxylauric acid anilide, 4-hydroxystearic acid anilide, N-(3,5-di-tert-butyl-4-hydroxyphenyl)carbamic acid octyl ester, and derivatives thereof; esters of .β.-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid with mono- or poly-hydric alcohols, for example with methanol, ethanol, n-octanol, isooctanol, octadecanol, 1,6-hexanediol, 1,9-nonanediol, ethylene glycol, 1,2-propanediol, neopentyl glycol, thiodiethylene glycol, diethylene glycol, triethylene glycol, pentaerythritol, tris(hydroxyethyl) isocyanurate, N,N'-bis(hydroxyethyl)oxalic acid diamide, 3-thiaundecanol, 3-thiapentadecanol, trimethylhexanediol, trimethylolpropane, 4-hydroxymethyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane, and derivatives thereof; esters of .β.-(5-tert-butyl-4-hydroxy-3-methylphenyl)propionic acid with mono- or poly-hydric alcohols, for example with methanol, ethanol, n-octanol, isooctanol, octadecanol, 1,6-hexanediol, 1,9-nonanediol, ethylene glycol, 1,2-propanediol, neopentyl glycol, thiodiethylene glycol, diethylene glycol, triethylene glycol, pentaerythritol, tris(hydroxyethyl) isocyanurate, N,N'-bis(hydroxyethyl)oxalic acid diamide, 3-thiaundecanol, 3-thiapentadecanol, trimethylhexanediol, trimethylolpropane, 4-hydroxymethyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane; 3,9-bis[2-{3-(3-tert-butyl-4-hydroxy-5-methylphenyl)propionyloxy}-1,1-dim- ethylethyl]-2,4,8,10-tetraoxaspiro[5.5]undecane, and derivatives thereof; esters of .β.-(3,5-dicyclohexyl-4-hydroxyphenyl)propionic acid with mono- or poly-hydric alcohols, for example with methanol, ethanol, octanol, octadecanol, 1,6-hexanediol, 1,9-nonanediol, ethylene glycol, 1,2-propanediol, neopentyl glycol,

thiodiethylene glycol, diethylene glycol, triethylene glycol, pentaerythritol, tris(hydroxyethyl)isocyanurate, N,N'-bis(hydroxyethyl)oxalic acid diamide, 3-thiaundecanol, 3-thiapentadecanol, trimethylhexanediol, trimethylolpropane, 4-hydroxymethyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane, and derivatives thereof; esters of 3,5-di-tert-butyl-4-hydroxyphenylacetic acid with mono- or poly-hydric alcohols, for example with methanol, ethanol, octanol, octadecanol, 1,6-hexanediol, 1,9-nonanediol, ethylene glycol, 1,2-propanediol, neopentyl glycol, thiodiethylene glycol, diethylene glycol, triethylene glycol, pentaerythritol, tris(hydroxyethyl)isocyanurate, N,N'-bis(hydroxyethyl)oxalic acid diamide, 3-thiaundecanol, 3-thiapentadecanol, trimethylhexanediol, trimethylolpropane, 4-hydroxymethyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane, and derivatives thereof; amides of .beta.-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid, for example N,N'-bis(3,5-di-tert-butyl-4-hydroxyphenylpropionyl)hexamethylenediamide, N,N'-bis(3,5-di-tert-butyl-4-hydroxyphenylpropionyl)trimethylenediamide, N,N'-bis(3,5-di-tert-butyl-4-hydroxyphenylpropionyl)hydrazide), N,N'-bis[2-(3-[3,5-di-tert-butyl-4-hydroxyphenyl]-propionyloxy)ethyl]oxam- ide (Naugard.RTM. XL-1 from Uniroyal), and derivatives thereof; ascorbic acid (Vitamin C), and derivatives thereof; amine-type antioxidants, for example N,N'-di-isopropyl-p-phenylenediamine, N,N'-di-sec-butyl-p-phenylenediamine, N,N'-bis(1,4-dimethylpentyl)-p-phenylenediamine, N,N'-bis(1-ethyl-3-methylpentyl)-p-phenylenediamine, N,N'-bis(1-methylheptyl)-p-phenylenediamine, N,N'-dicyclohexyl-p-phenylenediamine, N,N'-diphenyl-p-phenylenediamine, N,N'-di(2-naphthyl)-p-phenylenediamine, N-isopropyl-N'-phenyl-p-phenylenediamine, N-(1,3-dimethyl-butyl)-N'-phenyl-p-phenylenediamine, N-(1-methylheptyl)-N'-phenyl-p-phenylenediamine, N-cyclohexyl-N'-phenyl-p-phenylenediamine, 4-(p-toluenesulfonamido)-diphenylamine, N,N'-dimethyl-N,N'-di-sec-butyl-p-phenylenediamine, diphenylamine, N-allyldiphenylamine, 4-isopropoxydiphenylamine, N-phenyl-1-naphthylamine, N-(4-tert-octylphenyl)-1-naphthylamine, N-phenyl-2-naphthylamine, octylated diphenylamine, for example p,p'-di-tert-octyl-diphenylamine, 4-n-butylaminophenol, 4-butyrylaminophenol, 4-nonanoylaminophenol, 4-dodecanoylaminophenol, 4-octadecanoylaminophenol, di(4-methoxyphenyl)amine, 2,6-di-tert-butyl-4-dimethylaminomethylphenol, 2,4'-diaminodiphenylmethane, 4,4'-diaminodiphenylmethane, N,N,N',N'-tetramethyl-4,4'-diaminodiphenylmethane, 1,2-di[(2-methylphenyl)amino]ethane, 1,2-di(phenylamino)propane, (o-tolyl)-biguanide, di[4-(1',3'-dimethylbutyl)phenyl]amine, tert-octylated N-phenyl-1-naphthylamine, mixture of mono- and di-alkylated tert-butyl-/tert-octyl-diphenylamines, mixture of mono- and di-alkylated nonyl-diphenylamines, mixture of

mono- and di-alkylated dodecyidiphenylamines, mixture of mono- and di-alkylated isopropyl-/isohexyl-diphenylamines, mixtures of mono- and di-alkylated tert-butyidiphenylamines, 2,3-dihydro-3,3-dimethyl-4H-1,4-benzothiazine, phenothiazine, mixture of mono- and di-alkylated tert-butyl-/tertoctyl-phenothiazines, mixture of mono- and di-alkylated tert-octylphenothiazines, N-allylphenothiazine or N,N,N',N'-tetraphenyl-1,4-diaminobut-2-ene, and derivatives thereof.

Embodiments of the coupling process of the present invention may comprise any ATRP initiator thereby providing a great selection of R-groups on the formed nitroxide. An ATRP initiator may be any ATRP initiator, such as a chemical molecule or functionalized particle with a transferable (pseudo)halogen that can form an active radical species. Many different types of halogenated compounds, for example, are potential ATRP initiators. In prior art references, many ATRP initiators are described. The ATRP initiator may have a low molecular weight or a high molecular weight such as a macromolecule and/or comprise a solid particle, or a surface, for example. In certain embodiments, ATRP initiators may comprise at least two radically transferable atoms or groups or be a polymer or a solid.

Embodiments of the method of the present invention may be performed in bulk or in a solvent. If a solvent is used, the solvent may be a protic media or a non-protic media. A protic media is a media that comprises at least one component that is capable of being a proton donor. The protic media may comprise water and at least one alcohol, for example. The alcohol of the protic media may be, for example, methanol, ethanol, propanol, isopropanol, butanol, isobutanol, heptanol, or mixtures thereof.

Embodiments of the present invention also include coupling reactions conducted in non-protic media, wherein the non-protic media comprises an aromatic solvent, such as, but not limited to, anisole, xylene, benzene, a halogenated benzene derivative, or other nonprotic solvents.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a polymer" may include more than one polymer.

Unless otherwise indicated, all numbers expressing quantities of ingredients, time, temperatures, and so forth used in the present specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the

application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, may inherently contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

It is to be understood that this invention is not limited to specific compositions, components or process steps disclosed herein, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

The term "inert" refers to a substituent or compound means that the substituent or compound will not undergo modification either (1) in the presence of reagents that will likely contact the substituent or compound, or (2) under conditions that the substituent or compound will likely be subjected to (e.g., chemical processing carried out subsequent to attachment an "inert" moiety to a substrate surface).

The term "available" to refer to an optionally substituted carbon atom refers to a carbon atom that is covalently bound to one or more hydrogen atoms that can be replaced by a designated substituent without disrupting or destabilizing the remaining structure of the molecule.

"Optional" or "optionally" means that the subsequently described circumstance may or may not occur and is not necessary, so that the description includes instances where the circumstance occurs and instances where it does not. For example, the phrase "optionally substituted" means that a non-hydrogen substituent may or may not be present, and, thus, the description includes structures wherein a non-hydrogen substituent is present and structures wherein a non-hydrogen substituent is not present.

The term "radical" encompasses all non-ionic active radical based species formed by homolytic cleavage of a bond and is not limited to a carbon centered free radical that does not interact with any other component in the system.

Preferably, the ligand(s) which should in certain embodiments at least partially preferentially solubilize both oxidation states of the catalyst into the reaction medium while forming a catalyst complex with appropriate activity. The ligand for the transition metal complex may also facilitate removal of the transition metal from the organic phase after the

reaction has been completed. A ligand with some hydrophilic character, particularly when complexed with the higher transition state transition metal, can cause the higher oxidation state of the transition metal complex to migrate from an organic phase to a contacting aqueous phase. Further the transition metal complex can separate from the aqueous phase as a solid, thereby providing a means to recycle the transition metal. For example, during the reaction, the transition metal complex in the higher oxidation state is converted to the lower oxidation state by the reducing agent and migration is minimized. After the reaction is complete exposure to air forms the higher oxidation state catalyst and enhances migration to a contacting aqueous phase. Indeed in bulk or solution reactions water may be added at the end of the reaction solely to remove the complex. The catalyst may then separate out as a solid and be readily recycled. The resulting alkoxyamine is essentially colorless.

The process of the invention can be conducted in a biphasic system. Typically, it is preferable for the lower oxidation state of the transition metal complex to be at least partially soluble in the dispersed phase while the higher oxidation state may be less soluble in the dispersed phase. A water-soluble reducing agent may be preferred for embodiments of the present ATRC invention since the higher oxidation state transition metal would be reduced in the aqueous phase and driven back to the organic phase. An example of how the reducing agents can be selected to be additionally environmentally benign would be a combination of ascorbic acid or vitamin C and a sugar for a biphasic coupling process may require less than 100 ppm transition metal complex as the catalyst.

The amount of reducing agent, or agents, that is required to be added to the reaction can be approximated by consideration of the moles of initiator added to the reaction plus the amount of transition metal added to the reaction and the expected level of impurities in the system.

Example 1.

In the following example the ratio of transition metal to "initiator" is 100:1. An excess of stable free radical is added to the reaction to clearly demonstrate quantitative conversion of the "initiator" to the alkoxyamine.

Ethyl-2-bromoisobutyrate, 0.10 mL (0.68 mmol); TEMPO, 0.128 g (0.82 mmol); $CuBr_2$, 0.0015 g (0.0068 mmol); dNbpy, 0.0056 g (0.0136 mmol) and toluene, 2.0 mL were added sequentially to a 10 mL Schlenk flask. The system was deoxygenated by bubbling nitrogen through the solution for 40 minutes. The flask was then heated to 60 °C before a deoxygenated toluene solution (0.4 mL) of tin 2-ethylhexanoate (0.276 g, 0.68 mmol) was injected to initiate the reaction. After 14 hours, the reaction was exposed to air and subject to

^{1}HNMR analysis. The chemical shift of the methyl protons close to carbonyl group completely shifted from 1.92 ppm to 1.46 ppm, which indicated complete reaction of ethyl-2-bromoisobutyrate to form the alkoxyamine; ethyl 2-(2,2,6,6-tetramethylpiperidinyloxy)isobutyrate.

We claim the novel procedure disclosed herein, exemplified by an improved method for the preparation of alkoxyamines from nitroxides, comprising conducting an atom transfer radical addition reaction between an ATRP initiator and a molecule capable of reacting with the formed radical in the presence of a catalytic amount of a transition metal complex and a reducing agent. Other obvious extensions of these embodiments to other atom transfer addition reactions are also covered.

Other catalytic addition reactions can also be activated by the presence of a reducing agent. An example is the reaction gaining increased attention for linking two molecules the "click" reaction the use of hydrazine as a reducing agent for click reactions. Reactions conducted using CuBr/Me_6TREN as the catalytic complex under limited air are fast and efficient even without any reducing agent when the catalyst concentration is 50 mol% relative to azide and acetylene end groups. However, if the catalyst concentration was lowered, a reducing agent would probably be needed to prevent the oxidation of such reducing catalysts. Therefore additional reactions were conducted in the same manner as previously described, but this time using five times less catalyst than usually employed (PG-02-42). The components of the reaction mixtures were added in the following amounts:

$pS(N_3)_2$ ⇨ 0.1272 g ⇨ M_n = 2545 g/mol ⇨ 0.10 mmol N_3

Pg_2O ⇨ 5.15 μL ⇨ d = 0.913 g/mL ⇨ Mw = 94.11 g/mol ⇨ 0.10 mmol acetylene

CuBr ⇨ 0.0014 g ⇨ Mw = 143.45 g/mol ⇨ *0.10*[N_3]

Me_6TREN ⇨ 2.64 μL ⇨ d = 0.873 g/mL ⇨ Mw = 230.39 g/mol ⇨ 0.10[N_3]

DMF ⇨ 1.0 mL

1 ⇨ hydrazine ⇨ 0.78 μL ⇨ d = 1.021 g/mL ⇨ Mw = 32.05 g/mol ⇨ 2.5[CuBr]

2 ⇨ no hydrazine

3 ⇨ large excess of hydrazine ⇨ 3.9 μL ⇨ 12.5[CuBr]

The results of these reactions are shown in Figure 5.

When the catalyst concentration is reduced to 10 mol% relative to azide and acetylene end groups, the reaction conducted in the presence of no hydrazine shows practically no change for 48 hours, presumably because all of the catalyst was oxidized. The

reaction conducted in the presence of a ten-fold excess of hydrazine relative to CuBr works, but more much more slowly than typical click reactions with Me_6TREN. However, a 50-fold excess of hydrazine allows these reactions to be conducted very quickly, with no attempts to exclude oxygen before the reaction, and in the presence of a low concentration of catalyst.

Analogous reactions were conducted using TPMA as the ligand. The components of these reactions were added in the following amounts:

$pS(N_3)_2$ ⇨ 0.1272 g ⇨ M_n = 2545 g/mol ⇨ 0.10 mmol N_3
Pg_2O ⇨ 5.15 μL ⇨ d = 0.913 g/mL ⇨ Mw = 94.11 g/mol ⇨ 0.10 mmol acetylene
CuBr ⇨ 0.0014 g ⇨ Mw = 143.45 g/mol ⇨ 0.10[N_3]
TPMA ⇨ 0.0029 g ⇨ Mw = 290.36 g/mol ⇨ 0.10[N_3]
DMF ⇨ 1.0 mL
1 ⇨ hydrazine ⇨ 3.9 μL ⇨ d = 1.021 g/mL ⇨ Mw = 32.05 g/mol ⇨ 12.5[CuBr]
2 ⇨ no hydrazine

The reaction conducted in the presence of hydrazine worked, and even much more quickly than click reactions in the presence of CuBr/TPMA without hydrazine under oxygen-free conditions. The reaction conducted under limited air and without hydrazine did not appear to do anything for the first three hours, but the reaction then proceeded at a slower rate than typical click reactions with TPMA.

CLAIMS

1. A process for the preparation of alkoxyamines, comprising:

reacting an ATRP initiator and a nitroxide in the presence of a reaction medium comprising a reducing agent and at least one transition metal catalyst

wherein the molar ratio of the transition metal to the ATRP initiator is less than 0.5.

2. The process of claim 1, wherein the transition metal catalyst is in an oxidized state, and the process comprises reacting the reducing agent with at least one of the transition metal catalyst in an oxidized state and an ATRP initiator.

3. The process of claim 1, wherein the molar ratio of the transition metal to the ATRP initiator is less than 0.1.

4. The process of claim 1, wherein the molar ratio of the transition metal to the ATRP initiator is less than 0.05.

5. The process of claim 1, wherein the concentration of transition metal in the reaction medium is less than 1000 ppm.

6. The process of claim 1, wherein the concentration of transition metal in the reaction medium is less than 100 ppm.

7. The process of claim 1, wherein the concentration of transition metal in the reaction medium is less than 10 ppm.

8. The process of claim 1 wherein the molar ratio of the ATRP initiator to the reducing agent is greater than 1.

9. The proeess of claim 1, wherein the reaction medium further comprises a suspending medium.

10. The process of claim 1, wherein the reducing agent is an inorganic compound other than a transition metal in the zero oxidation state.

11. The process of claim 10, wherein the reducing agent is at least one of a transition metal compound, a sulfur compound of a low oxidation level, sodium hydrogen sulfite, an inorganic salt comprising a metal ion, hydrazine hydrate, and derivatives of such inorganic compounds.

12. The process of claim 11, wherein the metal ion is at least one of Sn^{2+}, Fe^{2+}, Cr^{3+}, Al^{3+}, Ti^{3+} and Ti^{4+}.

13. The process of claim 12, wherein the metal ion is at least one of Sn^{2+}, Fe^{2+}, Cr^{3+} and Ti^{3+}.

14. The process of claim 1, wherein the reducing agent is an organic compound.

15. The process of claim 14, wherein the reducing agent is at least one of alkylthiols, mercaptoethanol or carbonyl compounds that can be easily enolized, ascorbic acid, acetyl acetonate, camphosulfonic acid, hydroxy acetone, reducing sugars, monosaccarides, glucose, aldehydes, and derivates of such organic compounds.

16. The process of claim 1, wherein the ATRP initiator comprises at least two radically transferable atoms or groups.

17. The process of claim 1, wherein the ATRP initiator is a polymer or a solid.

18. The process of claim 1, wherein the reaction medium further comprises a solvent or suspending medium.

19. The process of claim 18, wherein the process is conducted in one of an emulsion, a mini-emulsion, a microemulsion process, a reverse emulsion, and a suspension process.

20. The process of claim 1, wherein the reducing agent is at least partially soluble.

21. The process of claim 1, wherein the transition metal catalyst participates in a redox reaction between a lower oxidation state and a higher oxidation state.

22. The process of claim 21, wherein the molar ratio of reducing agent to transition metal catalyst in the higher oxidation state is greater than 1.

23. The process of claim 1, wherein the ATRP initiator is at least one of an alkyl halide and a substituted ester.

24. The process of claim 19, wherein the reaction medium comprises a base.

25. The process of claim 1, wherein the ATRP initiator is attached to a substrate.

26. The process of claim 1, wherein the reducing agent is capable of reacting with dissolved oxygen or reacting with a transition metal complex that was oxidized by oxygen.

27. The process of claim 1 wherein the transition metal catalyst complex comprises a ligand.

28. The process of claim 1, wherein the reaction medium comprises two reducing agents.

29. The process of claim 29, wherein the rate of reduction of the two reducing agents is different.

30. The process of claim 18, wherein the ATRP initiator comprises at least two radically transferable atoms or groups.

31. The process of claim 19, wherein the reducing agent is soluble in at least one of the suspending medium and the reaction medium.

32. The process of claim 1, wherein the transition metal catalyst comprises a transition metal in the higher oxidation state and the molar ratio of reducing agent to total molar amount of initiator and transition metal in the higher oxidation state is greater than 1.

33. The process of claim 1, wherein the reaction medium comprises at least two different reducing agents.

34. The process of claim 34, wherein the rate of reduction of the two reducing agents is different.

35. The process of claim 1, wherein the reaction medium comprises a phase comprising the nitroxide and the concentration of the reducing agent in the phase comprising the nitroxide is less than 5 wt%.

36. The process of claim 35, wherein the concentration of the reducing agent in the phase comprising the nitroxide is less than 1 wt%.

37. The process of claim 35, wherein the concentration of the reducing agent in the phase comprising the nitroxide is less than 100 ppm.

38. The process of claim 37, wherein the reducing agent is ascorbic acid or a derivative of ascorbic acid.

39. The process of claim 1 wherein the transition metal catalyst is in at least one of the higher or lower oxidation state.

40. The process of claim 1 wherein the rate of the coupling reactions can be further tuned by the addition rate/amount or composition of the reducing agent.

41. The process of claim 1 wherein the rate of the process is controlled throughout the process by adjusting the Cu(I)/Cu(II) ratio through continuous addition of a reducing agent.

42. A process, comprising:

coupling an ATRP initiator and a stable free radical in the presence a reaction medium comprising:

at least one transition metal catalyst; and

a reducing agent; wherein the molar ratio of the transition metal catalyst to the ATRP initiator is less than 0.25.

43. The process of claim 42, wherein the mole ratio of the reducing agent to the ATRP initiator is greater than 1.

44. A process, comprising:

conducting an atom transfer radical reaction process in the presence of an organic reducing agent.

45. The process of claim 44, wherein the organic reducing agent is one of at least one of alkylthiols, mercaptoethanol or carbonyl compounds that can be easily enolized, ascorbic

acid, acetyl acetonate, camphosulfonic acid, hydroxy acetone, reducing sugars, monosaccarides, glucose, aldehydes, and derivates of such organic compounds.

46. The process of claim 45, wherein the organic reducing agent is ascorbic acid or a derivative of ascorbic acid.

47. The process of claim 44, wherein the atom transfer radical reaction process is one of atom transfer radical addition, atom transfer radical cyclization, atom transfer coupling, and atom transfer radical cyclization.

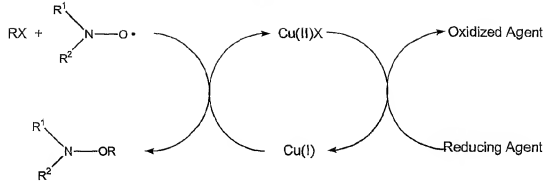


FIGURE 1A

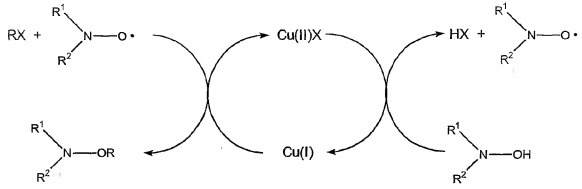


FIGURE 1B

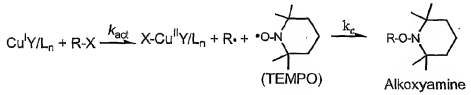


FIGURE 1C

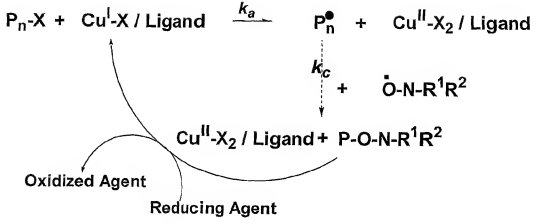


FIGURE 2

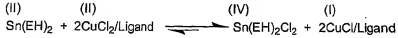


FIGURE 3

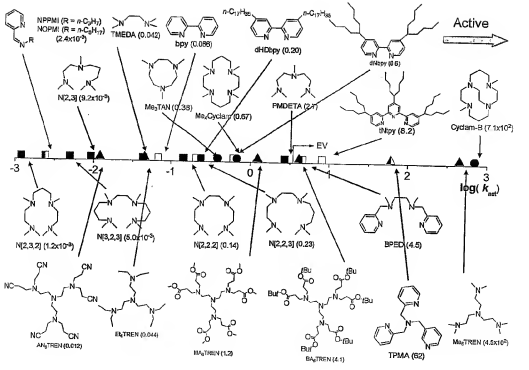

Active
TMEDA (0.042)
bpy (0.098)
dHDbpy (0.20)
dNbpy (9.6)
N(2,3) (9.2x10⁻³)
Me₆TAN (0.38)
Me₄Cyclam (0.67)
PMDETA (2.1)
Bpy (6.2)
Cyclam-B (7.1x10⁻²)
EV
-3
-2
-1
0
1
2
3
log(K_eq)
N(2,3,2) (1.2x10⁻³)
N(3,2,3) (5.0x10⁻³)
N(2,2,2) (0.14)
N(2,2,3) (0.23)
BPED (4.5)
AN₆TREN (0.012)
Et₆TREN (0.044)
Ba₆TREN (1.3)
Ba₃TREN (4.1)
TPMA (62)
Me₆TREN (4.5x10⁵)

FIGURE 4

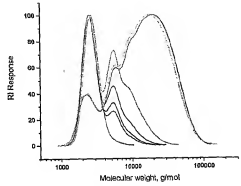


FIGURE 5A

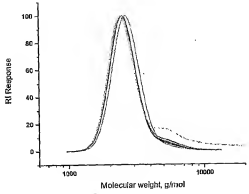
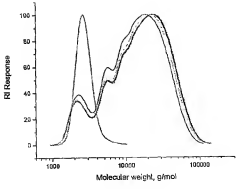


FIGURE 5B



Time	Area (%)	M_n	M_w/M_n
0.5 hr	80	11,201	1.64
1 hr	83	12,206	1.73
3 hrs	82	12,247	1.73
6 hrs	83	12,344	1.74
24 hrs	82	12,094	1.73
48 hrs	82	11,603	1.72

FIGURE 5C